REMARKS

Support for the amendments to the claims is shown in the following table:

Limitation	Specification Support
"wherein said (a) and (b) are conjugated by one or more covalent bonds."	Page 8, second paragraph.
"wherein said treatment is a cancer treatment."	Original claim 18.

Accordingly, no prohibited new matter has been added and entry of the amendment is respectfully requested.

I. Summary of the Office Action

Receipt of the previous response, filed 13 February 2003, has been acknowledged and amendments entered.

The Examiner has noted that the response was not fully responsive in view of compliance with sequencing rules.

Claims 16-18 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for being non-enabled.

Claims 1-3 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nagy et al. in view of Lu et al. and Taylor et al.

Claims 1-13, 15, and 16 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nagy et al. (1995) in view of Lu et al. (1994), Taylor et al. (1999), Anderson et al. (1999), Khan et al. (1997) Godard et al. (1995) and Ma et al. (1998).

II. Summary of Response

Applicants provide arguments and a Declaration under 37 C.F.R. §1.132 to rebut positions recited in the Office Action.

Applicants provide the appropriate Sequence Listing to comply with the rules as set forth in 37 C.F.R. §§1.821(a)(1) and (a)(2).

Applicants traverse the outstanding rejections against claims 1-13 and 16-18.

Applicants respectfully request reconsideration in view of the Declaration and arguments presented below.

III. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 16-18 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for non-enablement.

Claim 18 has been canceled, so the rejection as it might be applied against said claim is moot.

Applicants traverse the rejection as it applies against claims 16 and 17 for the reasons given below.

The focus of the present invention is the exploitation of somatostatin receptors to specifically target tissues for oligonucleotide uptake by cells in which the somatostatin receptor is over-expressed.

With respect to the state of the art, the major hurdle which has been identified in the references cited by the Examiner is drug (antisense) delivery. This is because for most antisense compounds, the oligonucleotide is delivered un-complexed (e.g., via intravenous injection), thus, all tissues may be targeted at random (i.e., no selectivity).

In past attempts to circumvent this problem, viral, retroviral and complexing oligonucleotides with lipids have been used. However, use of viral vehicles results in indiscriminant cell infection, or in the case of retroviral means, reduced target richness becomes an issue (i.e., only replicating cells can be targeted). Further, as stability of the oligonucleotide is of paramount import, viral and retroviral delivery means can only afford the use of phosphodiester-linked oligonucleotides, thus losing the ability to modify such oligonucleotide molecules.

While cationic liposomes as delivery means allow for use of chemically modified oligonucleotides, such systems have meet with very limited success (see for example, Schreier H., "The New Frontier: Gene and Oligonucleotide Therapy." Pharm Acta Helv (1994) 68(3):145-159).

The present invention remedies the delivery problem observed when using un-complexed, naked, vector delivered or liposome delivered oligonucleotides by using somatostatin-conjugates. Applicants have shown that drugs can be predictably delivered to selected sites within a living system (i.e., where SSTRs are expressed in vivo, see Table at page 27 of the instant specification).

The Examiner also stated that "a person skilled in the art would recognize that predicting the efficacy of an antisense compound in vivo is highly problematic." However, prediction of efficacy is not within the purview of the USPTO and, in fact, the Examiner's emphasis on toxicity, immunogenicity, dosing, and side effects are decisions "more properly left to the FDA." Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

Regarding the treatment envisaged by the present invention, such modalities couple overexpression of somatostatin receptors with particular disease states. Where such overexpression exists (e.g., breast cancer, peritumoral veins of human tumors, menigioma, gliomas, acute infectious diseases, and inflammatory cells), use of the envisaged conjugates as a treatment modality is contemplated.

Further, specific examples recited are enabled for oligonucleotides as disclosed which are known to be associated with tumors (e.g., bcl-2, c-raf 1, protein c-alpha, H-ras), since many have already been used in clinical trials showing initial efficacy (see, e.g., for bcl-2, <http://www.multiplemyeloma.org/treatments/3.04.01.asp>, last visited, 22 August 2003). The present invention provides a means for select delivery of such compounds to the tissue of interest.

Moreover, given the number of clinical trials on going, the predictability of efficacy would suggest that antisense oligonucleotides are at least capable of limiting disease progression.

Antisense Therapy	Intended Use	Development Stage
G3139, by Genta (1996).	To treat a variety of cancers, including: breast, colorectal, prostate, small-cell lung cancers, melanoma, non-Hodgkin's lymphoma.	In clinical trials.
GEM® 92, by Hybridon (1999).	To treat HIV infection and AIDS.	In clinical trials.
GEM® 231, by Hybridon (2002).	To treat solid cancerous tumors.	In clinical trials.
ISIS 2302, by ISIS Pharmaceuticals (2001).	To treat ulcerative colitis and psoriasis and to prevent kidney transplant rejection.	In clinical trials.
ISIS 2503, by ISIS Pharmaceuticals (2001).	To treat cancers.	In clinical trials.
ISIS 3521, by ISIS Pharmaceuticals (2000).	To treat cancers.	In clinical trials.
ISIS 5132, by ISIS Pharmaceuticals (1997).	To treat cancers.	In clinical trials.
Vitravene, by Ciba Vision and ISIS Pharmaceuticals (1998, approved).	To treat cytomegalovirus in AIDS patients.	Available in the US.

Such efforts (i.e., use of somatostatin analog-antisense conjugates that target tissues selectively) coupled with efficacy data for known antisense oligonucleotides, would provide one skilled in the art with the guidance to make and use the invention as claimed in vivo.

For these reasons, a prima facie case of non-enablement has not been made and Applicants respectfully request that the rejection be withdrawn.

IV. Rejection Under 35 U.S.C. §103(a)

A. Claims 1-3 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Nagy et al., in view of Lu et al., and Taylor et al.

The rejection does not apply to claims 1-3 because one of skill in their art would not expect to successfully achieve the invention as claimed.

Nagy et al. teach the delivery of a small molecule, i.e., doxorubicin (molecule weight 580), into the target cell.

It is known that molecular modifications on ligands may result in a drastic decrease of the binding affinity to the receptor. Nagy et al. report that cytotoxic SST conjugates displayed approximately 10 times lower binding affinities than their respective carriers, i.e., somatostatin analogs (page 1796, right column, first paragraph). However, the cytotoxic agents of Nagy et al. weigh only some hundreds of Da, whereas the oligonucleotides according to the present invention are larger than 5000 Da and it could be expected that the loading of a somatostatin analog with a much larger molecule [oligonucleotide] would result in a greater decrease in binding affinity.

As can be seen from the Declaration, there is a tenfold increase in tumor uptake of conjugates according to the invention compared with non-conjugated oligonucleotide. Further, the binding affinity of the carrier is not significantly (statistically) affected by conjugation. On the contrary, Nagy et al. report a 10 times lower binding affinity of various conjugates compared with their carriers. Therefore, the effective and specific uptake of somatostain conjugates having high molecular weights would not be expected in view the teachings of Nagy et al.

The Examiner stated that Applicant's arguments are contradictory regarding

Lu et al. To clarify the point, Lu et al. teach to prepare the conjugate according to the method reported by Wu et al. (see page 270 second paragraph, right column). Wu et al. (J Biol Chem 1987; 262:4429-4432) is enclosed for the Examiner's convenience.

Wu et al. teach the coupling of ligand (i.e., asialoglycoprotein), to a polycation (i.e., poly-L-lysine), and subsequently adding DNA to form a soluble ligand-polycation-DNA complex (see Abstract, first paragraph and page 4429, right column, second paragraph), as polycations have been shown to increase in vitro cellular uptake of nucleic acids (page 4431, right column, fourth paragraph, also Braasch et al. cited by the Examiner). Wu et al. further show that mixtures of the ligand and DNA in the absence of the polycation are not internalized into the cells (Fig. 3, lane 4). Thus, Wu et al., whose method is applied by Lu et al., clearly teach that the polycation poly-L-lysine is essential for the uptake of the conjugate. Hence, a combination of the teachings of Nagy et al. and Lu et al. would result in a conjugate made of a somatostain analog, poly-L-lysine and a oligonucleotide, not in a covalent somatostain analog-oligonucleotide conjugate as claimed in the present application.

Also, Wu et al. advise not to covalently couple the DNA to the ligand, because a covalent coupling might alter the DNA (page 4429, right column, lines 16 to 20 from the bottom). Thus, Lu et al., in connection with the Wu et al. reference, in fact, teach away from the conjugate as claimed in the present application which requires covalent coupling. Further, Lu et al. also suggest to have a polycation in the conjugate, as Lu et al. confirm that the method takes advantage of the complex between the poly(L)lysine and the DNA (page 269, right column, lines 21 to 24 from the bottom). However, according the present application, complexing the DNA with poly-L-lysine is not necessary feature.

Regarding whether there is support for "ionic," Lu et al. report that "there is a significant dissociation of the antisense from the conjugate" resulting in a higher concentration of the conjugate in the blood (page 274, right column, lines 27 to 30 from the bottom); "30% of the antisense DNA dissociated from the carrier (i.e., poly(L)lysine) 7 min. after injection" and "HPLC analysis demonstrated approximately 85% dissociation" of the complex (page 272, right column, lines 6 and 10 from the top). This clearly proves that the conjugates taught by Lu et al. are conjugated by an ionic noncovalent salt like coupling. However, for tumor targeting, which is the object of the present invention, a high concentration of the antisense compound in the tumor cell is desired, and antisense compounds circulating in the blood should be limited. Thus, a person skilled in the art would decide against a method using a soluble, noncovalently coupled conjugate, wherein 30 to 85% of the active substance dissociates from the carrier.

The Taylor reference does not cure the deficiencies identified in Nagy et al. or Lu et al.

Thus, for the reasons given above, a prima facie case of obviousness has not been make and Applicants respectfully request that the rejection be withdrawn.

B. Claims 1-13, 15 and 16 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nagy et al., in view of Lu et al., Taylor et al., Anderson et al. (1999), Khan et al. (1997), Godard et al. (1995), and Ma (1998).

Applicants traverse the rejection as it applies against claims 11-13, 15 and 16 for the reasons given below.

As stated above, one of skill in the art would not use the teachings of Nagy et al.

because the reduction in binding affinity upon conjugation would dissuade the skilled artisan interested in somatostatin receptor directed cell targeting from using such analogs. Thus, in view of Lu et al., the skilled artisan would have no motivation to substitute the teachings of Nagy et al. in view of Lu et al. since the conjugates of the latter reference would not be expected to suffer the reduction in binding affinity after conjugation, as is seen in Nagy et al. Moreover, the dissociation of the oligonucleotide from the carrier would not be desired based on the problem to be solved. In addition, the conjugate as claimed would not be expected to be achieved by one of skill in the art based on the combination of references (e.g., covalent-linked conjugate).

Further, Anderson et al. would have to be viewed in light of the available art (i.e., Nagy et al.). Thus, there would have to be a reasonable explanation for why one of ordinary skill in the art would choose Anderson et al. over Nagy et al., given the reduction in binding affinity seen in the latter reference for such analogs (i.e., expected activity). In the absence of such an explanation, only the teachings of the instant specification would demonstrate that octreotide conjugates show no change in binding affinity. Therefore, such a combination (i.e., Anderson et al. with the other cited references) would represent impermissible hindsight, or at best, provide an obvious-to-try rationale in light of evidence to the contrary (i.e., evidence from Nagy et al. that intimates such conjugates would have reduced binding affinity).

With respect to Lu et al., a person skilled in the art would not have been motivated to substitute the antisense compound taught by Lu et al. in place of the cytotoxin compound of the somatostatin analog conjugates as taught by Nagy et al., because the teaching of Lu et al. fails to satisfy the demands of the present application (see above).

Further, Lu et al. do not show that the internalized antisense DNA is able to act as an antisense DNA which down-regulates gene expression. Lu et al. fails to show any biological activity of the internalized DNA. Lu et al. show internalization of a 67-mer DNA (page 270, third paragraph) which is too large to hybridize selectively with a complementary sequence. Selective antisense compounds are normally not larger than 30-residues (see, for instance, Taylor et al.: p. 562, first paragraph; cited by the Examiner). However, biological activity of the antisense compound is requisite for any antisense strategy. Thus, Lu et al. fail to show that an antisense compound which has been internalized by receptor-mediated endocytosis is able to hybridize the complementary sequence which down-regulates gene expression. Lu et al. fails to show that their conjugates are specific to both to the target receptor and to the target gene sequence. On the contrary, Sun et al. (Peptides 23 [2002] 1557-1565, enclosed) demonstrate that administration of antisense conjugates according to the invention inhibits n-*myc* oncogene expression and also results in cell death (see Abstract, Tables 1 and 2). The conjugate as claimed is not derivable from the disclosure of Lu et al. Also, the ratio of the molecular weights between the ligand asialoglycoprotein-poly(L)lysine (66 kDa) to the antisense oligonucleotide (21,1 kDa) is about 3:1 in Lu et al., i.e., the ligand is about 3 times larger than the antisense DNA.

In the present invention the ratio of the molecular weights between the somatostain analog ligand (1,5 kDa) and the antisense DNA (.5 kDa) is at least 1:3.3, i.e., the ligand is at least 3 times smaller than the antisense DNA. Thus, a person skilled in the art could not conclude from the teaching of Lu et al. how the coupling of a 3 or more times larger DNA to a ligand would influence the binding affinity of the ligand as disclosed in Lu et al.

Consequently, it was completely non-obvious in view of Lu et al. whether the claimed invention could be internalized into tumor cells, because Lu et al. teach a complex comprising DNA and a polycation that is coupled non-covalently to the ligand.

Further, as stated in the previous Response, Lu et al. do not deal with the transport of compounds into tumors. Lu et al. teach the delivery of antisense DNA into normal cells, specifically liver cells.

Review of the Declaration demonstrates that the conjugated oligonucleotide is internalized more effectively in tumors than when unconjugated (e.g., compare uptakes for control conjugates between the kidney and tumor). Thus, the characteristics of normal tissue versus cancerous tissue for uptake of conjugated and non-conjugated oligonucleotides are in fact different. Therefore, a person skilled in the art would not consider Lu et al. for developing a tumor-selective delivery system for cancerous tissues.

Neither Ma et al., Taylor et al., Khan et al., nor Goddard et al. cure the deficiencies as outlined above. Accordingly, one of skill in the art would not be motivated to substitute the somatostain analog of Nagy et al. for the analogs of Anderson et al. because the skilled artisan would be dissuaded from using carriers that showed decreased binding affinity upon conjugation (i.e., expected activity). As Anderson et al., does not contradict the data of Nagy et al., i.e., that somatostain analogs of the type used in the present specification do not show reduced affinity. Such a conclusion only comes from the instant specification. Respectfully, this represents impermissible hindsight, or at best, the application of an erroneous obvious to try standard in the face of contradictory evidence.

Further, in view of the teachings of Nagy et al., one of skill in the art would not be motivated to substitute the asialoglycoprotein carrier for the somatostain analog because of the affinity data. The asialoglycoprotein carrier would not be expected to have reduced binding affinity upon conjugation as was seen for the Nagy et al. carrier (i.e., unless covalently combined, see Wu et al., supra).

In addition, given the characteristics of the Lu et al. conjugate (in view of Wu et al.), one of skill in the art would not use the teachings of Lu et al. to make a somatostatin conjugate in the absence of polycation, especially such a conjugate that is covalently bound. Again, the additional cited references do not cure these deficiencies.

Therefore, in view of the above, one of skill in the art would not be motivated to combine the cited references because the skill artisan would have no expectation of achieving the invention as claimed.

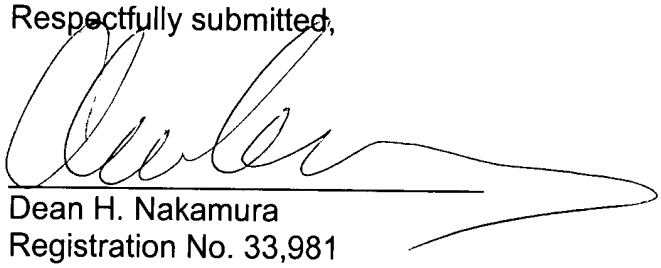
For these reasons, Applicants find that a prima facie case of obviousness has not been made and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. Reexamination, reconsideration, withdrawal of the objection and rejections, and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged to contact the undersigned at the local exchange noted below.

If any fees are found to be applicable, please charge any additional fees or make any credits to Deposit Account No. 07-1896.

Respectfully submitted,



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